Ethoxyacetic Acid

CAS #627-03-2
Swiss CD-1 mice, at 0.0, 0.2, 0.6, and 1.0% in water
James Lamb IV, NTP/NIEHS Project Officer
Dushyant Gulati, Leta Hommel, Valerie Russell, P.S. Sabharwal,
Environmental Health Research and Testing
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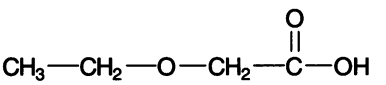

Ethoxyacetic acid (EAA), the active metabolite of 2-ethoxyethanol (a widely used glycol ether), was tested to assess its effects on reproduction in Swiss CD-1 mice using the RACB protocol (Morrissey et al., Fundam Appl Toxicol 13:747–777 [1989]). This was performed as part of a larger structure–activity program, evaluating numerous glycol ethers and their metabolites. From the range finding study (Task 1), doses of 0.2, 0.6, and 1.0% in water were selected for the continuous breeding phase of the study. These concentrations produced estimated average doses of approximately 303, 669, and 968 mg/kg/day.

Four female mice died during Task 2, two each in the middle and high dose groups. The deaths were due to partner-induced wounds. In Task 2, high dose mice gained less weight than the other mice so that at necropsy, body weights were reduced by approximately 13%. The number of litters per pair was reduced by 19% at the high dose, while the number of live pups per litter was decreased at both the middle dose (25%) and high dose (53%) levels. Adjusted live pup weight was reduced by 3% at the low dose and by 9% at the high dose. The mean adjusted live pup weight was the same value in the low and middle dose groups, but the variance was slightly higher for the middle dose group, making the difference from control not statistically significant. Cumulative days to litter increased by 5 to 9 days in the high dose group, an increase that was observed for all litters.

Task 4, the assessment of the second generation, was not conducted in this study (see the description in the introductory section).

Since adverse effects on fertility and reproduction were observed in Task 2, Task 3 (the crossover study) was conducted using the controls and high dose mice. In pairs with EAA-treated females, the number of live pups per litter decreased by 50% and adjusted live pup weight was reduced by 9%. Pairs with treated males were not different from controls.

After the evaluation of the Task 3 litters, the F_0 control and high dose adults were killed and necropsied. In EAA-treated females, relative kidney weight increased by 21%, while body weight was reduced by approximately 14%. The estrous cycle was approximately 15% longer in EAA-treated females than in controls (4.9 vs 5.6 days). In high dose males, body weight was approximately 12% less than controls, absolute testis weight was 13% lower than controls, while relative epididymis and seminal vesicle weights were reduced by 8 and 11%, respectively. For the high dose mice, the proportion of abnormal sperm increased from a control value of approximately 4% to 10%.

In conclusion, EAA had significant effects on both females and males. The increased estrous cycle length probably underlies the reduced number of litters per pair, while the Task 3 reduction in pups per litter and pup weight clearly mimics those effects seen in Task 2. The adverse effects on male reproductive organ weight and sperm morphology were not reflected in functional changes.

Summary: NTP Reproductive Assessment by Continuous Breeding Study.

NTIS#: **PB85197960/AS**
Chemical: **Ethoxyacetic Acid**
CAS#: **627-03-2**
Mode of exposure: **Water**
Species/strain: **Swiss CD-1 mice**

F_0 generation — Dose concentration →	0.2%	0.6%	1.0%
General toxicity	Male, female	Male, female	Male, female
Body weight	• , •	• , •	↓ , ↓
Kidney weight[a]	• , •	• , •	— , ↑
Liver weight[a]	• , •	• , •	— , —
Mortality	— , —	— , —	— , —
Feed consumption	• , •	• , •	• , •
Water consumption	• , •	• , •	— , —
Clinical signs	— , —	— , —	— , —
Reproductive toxicity			
x̄ litters/pair	—	—	↓
# live pups/litter; pup wt./litter	— , ↓	↓ , —	↓ , ↓
Cumulative days to litter	—	—	↑
Absolute testis, epididymis weight[a]	• , •	• , •	↓ , ↓
Sex accessory gland weight[a] (prostate, seminal vesicle)	• , •	• , •	— , ↓
Epidid. sperm parameters (#, motility, morphology)	• , •	• , •	— , — , ↑
Estrous cycle length	—	—	↑

Determination of affected sex (crossover)	Male	Female	Both
Dose level	—	1.0%	—

F_1 generation — Dose concentration →	10 ppm	30 ppm	60 ppm
General toxicity	Male, female	Male, female	Male, female
Pup growth to weaning	• , •	• , •	• , •
Mortality	• , •	• , •	• , •
Adult body weight	• , •	• , •	• , •
Kidney weight[a]	• , •	• , •	• , •
Liver weight[a]	• , •	• , •	• , •
Feed consumption	• , •	• , •	• , •
Water consumption	• , •	• , •	• , •
Clinical signs	• , •	• , •	• , •
Reproductive toxicity			
Fertility index	•	•	•
# live pups/litter; pup wt./litter	• , •	• , •	• , •
Absolute testis, epididymis weight[a]	• , •	• , •	• , •
Sex accessory gland weight[a] (prostate, seminal vesicle)	• , •	• , •	• , •
Epidid. sperm parameters (#, motility, morphology)	• , • , •	• , • , •	• , • , •
Estrous cycle length	•	•	•

Summary information	
Affected sex?	Female
Study confounders:	None
NOAEL reproductive toxicity:	<0.2%
NOAEL general toxicity:	0.6%
F_1 more sensitive than F_0?	Unknown
Postnatal toxicity:	Unknown

Legend: —, no change; •, no observation; ↑ or ↓, statistically significant change ($p<0.05$); — , —, no change in males or females. [a]Adjusted for body weight.